Breast cancer risk after recent childbirth: A pooled analysis of 15 prospective studies

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Abstract

Background: Parity is widely recognized as protective for breast cancer, but breast cancer risk may be increased shortly after childbirth. Whether this risk varies with breastfeeding, family history of breast cancer, or specific tumor subtype has rarely been evaluated.

Objective: To characterize breast cancer risk in relation to recent childbirth.

Design: Pooled analysis of individual-level data from 15 prospective cohort studies.

Setting: The international Premenopausal Breast Cancer Collaborative Group.

Participants: Women younger than 55 years.

Measurements: During 9.6 million person-years of follow-up, 18 826 incident cases of breast cancer were diagnosed. Hazard ratios (HRs) and 95% CIs for breast cancer were calculated using Cox proportional hazards regression.

Results: Compared with nulliparous women, parous women had an HR for breast cancer that peaked about 5 years after birth (HR, 1.80 [95% CI, 1.63 to 1.99]) before decreasing to 0.77 (CI, 0.67 to 0.88) after 34 years. The association crossed over from positive to negative about 24 years after birth. The overall pattern was driven by estrogen receptor (ER)-positive breast cancer; no crossover was seen for ER-negative cancer. Increases in breast cancer risk after childbirth were pronounced when combined with a family history of breast cancer and were greater for women who were older at first birth or who had more births. Breastfeeding did not modify overall risk patterns.

Limitations: Breast cancer diagnoses during pregnancy were not uniformly distinguishable from early postpartum diagnoses. Data on human epidermal growth factor receptor 2 (*HER2*) oncogene overexpression were limited.

Conclusion: Compared with nulliparous women, parous women have an increased risk for breast cancer for more than 20 years after childbirth. Health care providers should consider recent childbirth a risk factor for breast cancer in young women.

Primary Funding Source: The Avon Foundation, the National Institute of Environmental Health Sciences, Breast Cancer Now and the UK National Health Service, and the Institute of Cancer Research.

Breast cancer is the leading cancer diagnosis among reproductive-aged women worldwide (1). Parity is recognized as a protective factor for breast cancer overall, but this may largely apply to the peak ages of incidence (after age 60 years) and may not be true for younger women. Previous studies have reported that recent childbirth confers a short-term increase in breast cancer risk (2-13), which may last 10 or more years (6, 11, 14-16) and be amplified in women who are older at first birth (6, 11, 15, 16). Evidence for this increased risk often comes from national registry linkage studies in Scandinavian countries (2, 4, 6, 17). Information about such behaviors as breastfeeding is often not available or comes from case-control studies (8-11), where potential risk factors are assessed after diagnosis and parenting responsibilities could differentially deter study participation.

We used combined data from 15 cohort studies to assess breast cancer risk after childbirth. The use of international, prospective data offers a new opportunity to assess the strength and duration of associations between recent childbirth and breast cancer risk while considering the effect of such factors as breastfeeding and family history of breast cancer (5, 18). It also enables evaluation of risk that is specific to breast cancer subtypes that may be differentially influenced by reproductive history (12, 13, 19). Understanding these patterns may have implications for identifying risk-reducing strategies and vulnerable subgroups.

Methods

We used data from the Premenopausal Breast Cancer Collaborative Group, a pooling project involving 20 prospective cohort studies (20). This work was approved by the relevant institutional review boards.

In brief, participating studies contributed data from women aged younger than 55 years who did not have breast cancer at enrollment; these women were followed prospectively through direct contact or linkage with cancer registries (described previously [20]). Studies contributed (as available) age at enrollment and end of follow-up, demographic characteristics, lifestyle factors, reproductive history, medical conditions, and first-

degree family history of breast cancer at enrollment and each round of follow-up. Data harmonization and quality control were done by the study coordinating centers in North Carolina and London.

Across 15 cohorts that provided information on women's ages at childbirth (21-35), 890 269 women (96% of participants) had available information on total number of births and age at most recent birth or were nulliparous. We excluded women who reported a first birth before age 13 years (n = 82), were 50 years or older at study entry and at most recent birth (n = 60), or reached parity greater than 10 births before enrollment (n = 183). These events were considered to have greater potential for data errors. This left 889 944 women for analysis (**Supplement Figure 1**).

Attained age, ages at first and most recent births, and parity at study enrollment were available in all 15 studies (21-35). Twelve studies (21-27, 29, 31, 33-35) assessed pregnancy history in at least 1 follow-up questionnaire after enrollment; the remaining 3 provided pregnancy information at enrollment only. Breastfeeding status was available in 12 studies (21-23, 25-27, 29-34) and family history in 13 (21-27, 29, 31-35). Thirteen studies (21-23, 25-27, 29-35) reported breast cancer stage and estrogen receptor (ER) status.

Statistical Analysis

Parity, time since most recent birth, breastfeeding and family history of breast cancer were analyzed as time-varying exposures over follow-up. We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% CIs for the association between time since most recent birth and breast cancer, with attained age as the underlying time scale (17, 36). Follow-up started at age at study enrollment or the first available follow-up round with information on age at most recent birth and ended at breast cancer diagnosis, death, last follow-up, or age 55 years, whichever occurred first. During follow-up, women were censored at the age at which they reached parity greater than 10 births (n = 22) or the age at which they had a birth at age 50 years or older (n = 9) (**Supplement Figure 1**). Proportional hazards assumptions were assessed by Schoenfeld residuals (37) and were not significantly violated.

We first examined study-specific estimates and calculated a pooled estimate across studies using a random-effects model that weighted estimates by the inverse of the study-specific variance (38-40). Because we detected no significant heterogeneity between studies with the Cochran Q test or I^2 statistic (41-43) (**Supplement Figure 2**), we pooled individual-level data and did an aggregated analysis stratified by study cohort. **Supplement Table 1** gives characteristics of the individual cohorts.

Time since most recent birth and parity were modeled as time-varying exposures in 1-year and 1-birth increments, respectively. We accounted for additional births during follow-up by resetting time since birth to 0 at the time of each birth. The **Supplement** gives additional detail on these methods. Quadratic splines (44) were used to examine time since birth as a continuous, nonlinear exposure, defining time with knots at the 5^{th}, $25^{th,}$ $50^{th,}$ 75^{th}, and 95^{th} percentiles for the distribution of time since most recent birth for women with a breast cancer diagnosis before age 55 years. In spline models, time since most recent birth was set to 0 for nulliparous women and an indicator term for parity allowed the risk at 0 years since most recent birth to differ between nulliparous and parous women. As an approximation of the 95% CI (in years since most recent birth) for the point where the HR crossed 1.0, we used the points where the lower and upper bounds of the 95% CI for the spline regression crossed 1.0. In categorical models, exposure was defined as nulliparous or 0 to 2.9, 3 to 4.9, 5 to 9.9, 10 to 14.9, 15.0 to 19.9, 20.0 to 24.9, 25.0 to 29.9, or 30 or more years since most recent birth.

Covariates considered as potential confounders were parity, age at first birth, breastfeeding, infertility, education, oral contraceptive use, and birth cohort. We identified confounding variables using a directed acyclic graph (45, 46) and the prior literature (**Supplement Figure 3**); the minimally sufficient adjustment set was parity and breastfeeding. All models were adjusted for attained age (as the time scale; continuous), study, and parity (1 to 10 births; time-varying). Adjustment for breastfeeding was possible only in analyses limited to the 12 studies with available breastfeeding data.

We evaluated potential effect modification by parity (primiparous [1 birth], biparous [2 births], or multiparous [≥3 births]), age at first birth (<25, 25 to 34, or 35 to 39 years), breastfeeding, and family history of

breast cancer. Interactions between these factors and time since most recent birth were assessed using likelihood ratio tests (47). We examined risk for invasive nonmetastatic disease (stage I to III breast cancer) by treating breast cancer of stage 0 (in situ) or IV as a censoring event. Augmentation models were used to assess differences in HRs by ER status by using the Wald test (48).

In additional analyses, we restricted the cohort to parous women only, censored follow-up at age 45 years or the last age at which pregnancy history was assessed if younger than 45 years (to minimize the potential for additional pregnancies after the most recent questionnaire), excluded each study in turn to identify potentially influential studies, and excluded women with multiple births (for example, twins).

We also calculated the weighted cumulative incidence of breast cancer according to attained age for categories of time since most recent childbirth (nulliparous and 0 to 2.9, 3 to 6.9, 7 to 14.9, 15 to 24.9, and 25 or more years), adjusted for the distribution of parity in the overall pooled sample using an inverse probability of exposure approach, described further in **Supplement Figure 4** (49). Because our data were left-truncated, we also provided a standardized weighted cumulative incidence function calculated over a common age interval that had participants in each category of time since most recent birth. The standardized weighted cumulative incidence function starts at 0 at the beginning of the common age interval and cumulates throughout the interval, which allows comparison of the cumulative incidence across categories of time since most recent birth (**Supplement Figure 5**).

Analyses were done with SAS, version 9.3 (SAS Institute); figures were produced in SAS and R (R Foundation for Statistical Computing).

Role of the Funding Source

The funding sources for this analysis had no role in the design, conduct, or interpretation of the study.

Results

During 9 625 727 person-years of follow-up (mean, 10.8 years [SD,6.4]), 18 826 incident cases of breast cancer were diagnosed before age 55 years among 889 944 women. At enrollment, 720 555 women were parous; 71 609 women contributed 1 or more births during follow-up. The mean age at study entry was 41.8 years (range, 16.0 to 54.9 years). The last update of pregnancy information occurred at a mean age of 50.0 years (range, 16.0 to 76.7 years). Overall, 12.4% of person-years were contributed by women who reported a family history of breast cancer (**Table**). For parous women, 72.9% of person-years were contributed by women who reported breastfeeding.

Figure 1 shows the association between time since most recent birth and breast cancer risk, modeled nonlinearly as a continuous exposure. Compared with nulliparous women, parous women had an HR for breast cancer associated with time since most recent birth that peaked 4.6 years after birth (HR, 1.80 [95% CI, 1.63 to 1.99]) before decreasing to its lowest observed point (HR, 0.77 [CI, 0.67 to 0.88]) 34.5 years after birth; the crossover in risk occurred 23.6 years (CI, 21.9 to 25.0 years) after birth. Over a common age interval starting at age 41.5 years, the standardized cumulative incidence of breast cancer per 100 000 women among nulliparous women was 620 at age 45.0 years, 1252 at age 47.5 years, and 1955 at age 50.0 years. For comparison, the standardized cumulative incidence among women who had their most recent child 3 to 6.9 years before was 661 at age 45.0 years, 1422 at age 47.5 years, and 2202 at age 50.0 years (**Supplement Figure 5**). This corresponds to 41, 170, and 247 excess cases of breast cancer per 100 000 women at each respective age for women whose most recent birth was 3 to 6.9 years before, compared with nulliparous women.

The association between time since most recent birth and breast cancer risk was modified by family history of breast cancer ($P = 0.044$). **Supplement Figure 6** shows analyses done separately for women who did and did not have such a history. The peak HRs associated with time since most recent birth were 1.74 (CI, 1.54 to 1.96) at 4.6 years after birth for women without a family history and 1.82 (CI, 1.48 to 2.24) at 4.9 years in women with a family history. However, compared with women with neither risk factor (that is, nulliparous women without a family history of breast cancer), those with both (parous women with a family history) had a peak HR for breast cancer of 3.53 (CI, 2.91 to 4.29) at 4.9 years after birth (**Figure 2**).

We observed significant heterogeneity in the association between time since most recent birth and breast cancer risk according to age at first birth (P = 0.013) (**Figure 3**) and parity (P = 0.030) (**Figure 4**), but not breastfeeding (P = 0.38) (**Supplement Figure 7**). Peak HRs for breast cancer associated with recent childbirth seemed to be higher with increasing age at first birth; women in the youngest group at first birth (<25 years) did not have an increased risk for breast cancer compared with nulliparous women **(Figure 3).** The magnitude of peak HRs was smaller than that seen overall owing to the inability to adjust for parity continuously (1 to 10 births) across age-at-first-birth groups because few women who were older at first birth had 3 or more children. When primiparous, biparous, and multiparous women were evaluated separately, the magnitude of peak HRs was greatest (and the time to crossover toward an inverse association longest) among multiparous women (**Figure 4**).

The association between time since most recent birth and breast cancer risk differed by ER status (P < 0.001) (**Figure 5**). Risk for ER-negative breast cancer was highest 2.2 years after birth (HR, 1.77 [CI, 1.34 to 2.33]) and decreased to an HR of 1.38 (CI, 1.01 to 1.88) at 34.5 years after birth but did not cross over to a protective association. The pattern for ER-positive breast cancer, which accounted for 76% of all breast cancer cases, was similar to the overall results. Additional adjustment for breastfeeding history changed results only slightly for ER-negative breast cancer risk and did not detectably change ER-positive risk (**Supplement Figure 8**). In risk models for ER-negative breast cancer, the test for interaction between time since most recent birth and breastfeeding was statistically significant (P = 0.020). Risk for ER-negative cancer was generally higher for parous women compared with nulliparous women, regardless of breastfeeding status, although the pattern of risk with increasing time since most recent childbirth was less consistent among women who never breastfed, potentially because of smaller sample sizes (**Supplement Table 2**).

Supplement Table 3 shows analyses according to ER status and restricted to parous women. In models that defined the reference group as women 10 to 14.9 years from most recent birth, we continued to see a long-term crossover toward a protective association for ER-positive (but not ER-negative) breast cancer. Hazard

ratios for breast cancer were similar in models that included all breast cancer diagnoses (stages 0 to IV) or that censored in situ (stage 0) or distant (stage IV) diagnoses (**Supplement Table 4**).

Results were essentially unchanged in sensitivity analyses that censored women at the last age where pregnancy was assessed if it was less than 45 years (to minimize the potential for additional pregnancies after the most recent questionnaire), excluded 1 study at a time, or excluded multiple births (data not shown).

Discussion

Our analysis combined individual-level data from about 890 000 women from 15 prospective cohort studies across 3 continents to investigate breast cancer risk in reproductive-aged women. Compared with women who had not given birth, parous women had an elevated breast cancer risk that peaked around 5 years after childbirth and lasted about 20 years. Our results provide evidence that, overall, this association is not modified by breastfeeding and that it varies according to ER expression, age at first birth, parity, and family history of breast cancer.

To our knowledge, the effect of breastfeeding on breast cancer risk after childbirth has not been directly addressed before. Breastfeeding has been associated with an estimated 12% to 25% lower risk for premenopausal breast cancer overall (50, 51) and is thought to be particularly beneficial in reducing risk for ER-negative breast cancer, which is relatively more common at young ages than older ages. Although higher parity is associated with an overall increase in risk for ER-negative breast cancer (13, 52, 53), parous women who breastfeed have comparable risk to nulliparous women (13), suggesting that breastfeeding may mitigate parity-related increases in risk for ER-negative cancer.

In the current analysis of 12 international studies, risks for both ER-positive and ER-negative breast cancer were elevated for 20 years after most recent birth in parous compared with nulliparous women, regardless of breastfeeding. With longer follow-up, the expected inverse association between childbirth and breast cancer became apparent for ER-positive breast cancer, but risk remained elevated for ER-negative disease. These findings are consistent with a sustained increase in risk for ER-negative breast cancer for at least

25 years after birth in parous compared with nulliparous women, as reported in a pooled analysis of 4 U.S. studies that enrolled African American women (12). However, our findings disagree with that study's report of no increase in ER-positive breast cancer in the first 15 years after last birth.

Familial breast cancer tends to occur at a younger age than breast cancer in women without a genetic predisposition. Family history might therefore modify associations between recent childbirth and breast cancer risk. A study in Denmark (5) found stronger associations between recent childbirth (<5 years prior) and breast cancer risk among women with a mother or sister diagnosed with breast cancer than among those without. In Norway (18), short-term elevations in risk after childbirth were more apparent in women with a family history of breast cancer than in a common reference group of nulliparous women without such a history, although differences were not statistically significant. In our analysis, women who had given birth recently and had a family history of breast cancer had a 3.5-fold increase in breast cancer risk compared with women with neither characteristic.

The large number of cases in our pooled analysis allowed us to evaluate potential variation in the association between recent childbirth and breast cancer according to modifiable behaviors, familial susceptibility, and clinical subtypes. These considerations can rarely be addressed in individual studies because of the lower incidence and correspondingly small numbers of breast cancer diagnoses at young ages. However, calendar month was not uniformly available for ages at childbirth and breast cancer diagnosis, so we could not distinguish breast cancer cases diagnosed during pregnancy from those diagnosed in the months immediately postpartum. The small number of breast cancer cases and births that occurred at same integer age (n = 39) resulted in wide CIs for the HR estimate for the first year after childbirth. Our analyses do not address breast cancer risk after age 55 years because of limits of the data provided to the Premenopausal Breast Cancer Collaborative Group (20).

We did not address associations according to intervals between births; 1 prior study has suggested that longer intervals could magnify childbirth-related increases in breast cancer risk (17). Available breastfeeding

information was not specific to each birth; therefore, if women breastfed some children but not others, breastfeeding status may be misclassified for the most recent birth. Finally, we had limited data on *HER2* oncogene overexpression and did not evaluate whether associations differed by the *HER2* status of the tumor. In a case-only study of Hispanic women, those within 10 years of their last full-term pregnancy (vs. >10 years) had higher risk for *HER2*-positive disease (OR, 1.78 [CI, 1.08 to 2.93]) compared with ER and/or progesterone receptor positive/HER2- disease (19).

Several biological explanations for an increase in breast cancer risk after childbirth have been proposed. Proliferation of breast cells during pregnancy could promote accelerated development of latent initiated tumor cells (46, 54). In this way, a greater magnitude of risk conferred by older age at first birth could be due to a higher proportion of initiated cells at older ages. The postpartum breast microenvironment, characterized by lactational involution, may also facilitate cancer cell migration and metastasis; the observation that breast tumors diagnosed postpartum have more advanced stages at diagnosis than those diagnosed during pregnancy supports this mechanism (55-58). Although the higher proportion of advanced-stage tumors could also be due to less timely detection of breast cancer in lactating women, our similar results in analyses limited to stage I to III cancer and stratified by breastfeeding suggest that differential detection after childbirth is not the sole cause.

Breast cancer is the most common cancer type in reproductive-aged women. We report an increased risk for breast cancer after childbirth that can last more than 20 years. This risk may be enhanced when a woman is older at first birth, multiparous, or has a family history of breast cancer, and it is not mitigated by breastfeeding. Women and health care professionals should take these factors into account when considering individual risk profiles for breast cancer.

From University of North Carolina Gillings School of Global Public Health, Chapel Hill, North Carolina (H.B.N., J.C., J.X.); The Institute of Cancer Research, London, United Kingdom (M.J.S., L.B.W., M.N.B., M.E.J., A.J.S.); Karolinska Institutet, Stockholm, Sweden (H.A.); University of Pisa, Pisa, Italy (L.B.); Slone Epidemiology Center at Boston University, Boston, Massachusetts (K.A.B., J.R.P.); Vanderbilt-Ingram Cancer Center and Vanderbilt University School of Medicine, Nashville, Tennessee (W.J.B., W.Z.); Institut National de la Santé et de la Recherche Médicale (INSERM) U1018 and Institut Gustave Roussy Centre for Research in Epidemiology and Population Health, Villejuif, France (M.B.); Public Health Direction and Biodonostia Research Institute and Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública, Basque Regional Health Department, San Sebastian, Spain (M.D.); International Agency for Research on Cancer, Lyon, France (L.D.); Brigham and Women's Hospital, Harvard Medical School, and Harvard T.H. Chan School of Public Health, Boston, Massachusetts (A.H.E., R.M.T.); Cancer Council Victoria and University of Melbourne School of Population and Global Health, Melbourne, Victoria, Australia (G.G.G., R.L.M.); University of Tromsø, The Arctic University of Norway, Tromsø, Norway (I.T.G.); University of Massachusetts Amherst School of Public Health and Health Sciences, Amherst, Massachusetts (S.E.H.); Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (J.H.); German Cancer Research Center, Heidelberg, Germany (R.K.); University of Oxford, Oxford, United Kingdom (T.J.K.); National Cancer Institute, National Institutes of Health, Bethesda, Maryland (C.M.K., M.L.); Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (S.C.L., A.W.); School of Public Health, Imperial College London, London, United Kingdom (M.A.M., E.R.); Cancer Registry of Norway, Institute of Population-Based Cancer Research, and University of Oslo, Oslo, Norway, and University of Southern California, Los Angeles, California (V.P.); University Medical Center Utrecht, Utrecht, the Netherlands (P.H.P.); Umeå University, Umeå, Sweden (M.S.); Danish Cancer Society Research Center, Copenhagen, Denmark (A.T.); Hellenic Health Foundation, Athens, Greece (A.T.); Norwegian University of Science and Technology, Trondheim, Norway (G.U., L.V.); Johns Hopkins Bloomberg School of Public Health and Johns Hopkins School of Medicine, Baltimore, Maryland (K.V.); Karolinska Institutet, Stockholm, Sweden, University of Tromsø, The Arctic University of Norway, Tromsø, Norway, and Folkhälsan Research Center, Helsinki, Finland (E.W.); and National Institute of Environmental Health Sciences, National Institutes of Health, Durham, North Carolina (C.R.W., D.P.S.)

Acknowledgment: The authors thank all study participants, staff, and participating cancer registries, as well as Chelsea Anderson, Niclas Håkansson, Melissa House, and Allison Iwan. The Nurses' Health Study and Nurses' Health Study II thank study participants, staff, and the following state cancer registries: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming. The Black Women's Health Study obtained pathology data on breast cancer from state cancer registries in Arizona; California; Colorado; Connecticut; Delaware; Washington, DC; Florida; Georgia; Illinois; Indiana; Kentucky; Louisiana; Maryland; Massachusetts; Michigan; New Jersey; New York; North Carolina; Oklahoma; Pennsylvania; South Carolina; Tennessee; Texas; and Virginia. The authors assume full responsibility for analyses and interpretation of these data. They thank the National Cancer Institute Cohort Consortium for facilitating this collaboration.

Financial Support: In part by the Avon Foundation (02-2014-080); funding from Breast Cancer Now and the U.K. National Health Service to the Royal Marsden–Institute of Cancer Research National Institute for Health Research Biomedical Research Centre; the Institute of Cancer Research, London; the National Institute of Environmental Health Sciences (Z01 ES044005) and National Cancer Institute (UM1 CA176726, UM1 CA186107, UM1 CA164974, R01 CA058420, R01 CA092447, and P50 CA168504) of the National Institutes of Health; the National Center for Advancing Translational Sciences (KL2-TR001109); the National Program of Cancer Registries of the Centers for Disease Control and Prevention and the Department of Energy; the Swedish Research Council and Swedish Cancer Society; the Japanese Ministry of Health, Labour and Welfare;

the Hellenic Health Foundation; a Karolinska Institutet Distinguished Professor Award (2368/10-221); Cancer Council Victoria and the Australia National Health and Medical Research Council (209057, 396414, and 504711); the state of Maryland; and the Maryland Cigarette Restitution Fund. The coordination of EPIC (the European Prospective Investigation into Cancer and Nutrition) is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by the Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Ge´ne´rale de l'Education Nationale, and Institut National de la Sante´ et de la Recherche Me´dicale (France); German Cancer Aid, German Cancer Research Center, and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sport, Netherlands Cancer Registry, LK Research Funds, Dutch Prevention Funds, Zorg Onderzoek Nederland, World Cancer Research Fund, and Statistics Netherlands (the Netherlands); ERC-2009-AdG 232997, Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, regional governments of Andaluci´a, Asturias, Basque Country, Murcia, and Navarra, and ISCIII RETIC (RD06/ 0020) (Spain); Swedish Cancer Society, Swedish Research Council, and county councils of Skåne and Va¨sterbotten (Sweden); and Cancer Research UK (14136 to EPIC-Norfolk and C570/ A16491 and C8221/A19170 to EPIC-Oxford) and the Medical Research Council (1000143 to EPIC-Norfolk and MR/M012190/1 to EPIC-Oxford) (United Kingdom).

Disclosures: Dr. Schoemaker reports grants from the United Kingdom–based charity Breast Cancer Now during the conduct of the study. Dr. Cai reports grants from the Avon Foundation during the conduct of the study. Ms. Wright reports grants from Breast Cancer Now during the conduct of the study. Dr. Jones reports grants from Breast Cancer Now during the conduct of the study. Dr. Giles reports grants from the National Health and Medical Research Council during the conduct of the study. Dr. Key reports grants from Cancer Research UK during the conduct of the study. Dr. Milne reports grants from the Australian National Health and Medical Research Council during the conduct of the study. Dr. Swerdlow reports grants from Breast Cancer Now during the conduct of the study. Authors not named here have disclosed no conflicts of interest.

Reproducible Research Statement: Study protocol: Published in reference 20. Statistical code and data set: Not available.

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